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Magnetic Resonance Imaging of the Central Nervous System in Diabetic Neuropathy

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Abstract Diabetic 'peripheral' neuropathy (DPN) is one of the common sequelae to the development of both type-1 and type-2 diabetes mellitus. Neuropathy has a major negative impact on quality of life. Abnormalities in both peripheral vasculature and nerve function are well documented and, in addition, evidence is emerging regarding changes within the central nervous system (CNS) that are concomitant with the presence of DPN. The often-resistant nature of DPN to medical treatment highlights the need to understand the role of the CNS in neuropathic symptomatology and progression, as this may modulate therapeutic approaches. Advanced neuroimaging techniques, especially those that can provide quantitative measures of structure and function, can provide objective markers of CNS status. With that comes great potential for not only furthering our understanding of involvement of the CNS in neuropathic etiology but also most importantly aiding the development of new and more effective, targeted, analgesic interventions.

Keywords Diabetic peripheral neuropathy · Neuroimaging · Magnetic resonance imaging · Brain · Spine · Central nervous system

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Introduction

One of the main motives for seeking medical advice that subsequently leads to a diagnosis of diabetes mellitus relates to the presence of symptoms and signs associated with painful diabetic polyneuropathy (painful-DPN) [1]. It has been previously documented that at some stage up to a fifth of all people with diabetes develop painful-DPN [2, 3]. Given such a high prevalence, coupled with the rapid increase in the number of people who are developing type-2 diabetes (T2DM), medical, social and economically devastating issues are expected. The alarming, younger age of those developing T2DM may in future also compound the extent of DPN. Although symptomatology can be mixed and wide-ranging in nature (perhaps potentially reflecting complexity in underlying pathological mechanisms) painful-DPN causes moderate to severe unremitting lower-limb pain in over 70 % of sufferers [3, 4] and leads to a loss of sleep [5]. It is hardly surprising that patients experience a reduction in their daily activities [6] and loss of employment [7], which are likely to heighten the incidence of depression, contributing to a poor quality of life [8]. Neuropathy and its complications are reported to account for over a quarter of the direct medical costs of diabetes [2]. The burden of painful-DPN is considerable, with most patients perceiving moderate to high levels of pain despite polypharmacy [7]. Thus, despite the high use of medical resource, current treatments are only partially effective [1], which reportedly at best provide 50 % pain relief in one third of patients [9]. A fundamental reason for the lack of effective therapeutic intervention is most likely based on the lack of knowledge of the underlying, causal pathophysiology [10, 11]. Thus, there is a clear need to unravel what, why, where, how, and when changes occur that may lead to anatomical and physiological disruption that are linked with symptoms and signs that fall under the umbrella of DPN.

Peripheral Abnormalities

The pathogenesis of DPN remains undetermined despite some considerable research, especially at the peripheral level of the nervous system [12, 13]. Morphometric studies have demonstrated that DPN is characterized by: (I) distal axonal loss [14]; (II) reduction in myelinated fiber density [15], and (III) focal areas of demyelination on teased fiber preparations [14]. Severe neural microvascular disease has also been demonstrated in clinical DPN [16–18]. Basement membrane thickening of endoneurial capillaries, degeneration of pericytes and hyperplasia and swelling of endothelial cells and sometimes microvessel closure have also been reported by several centers [16–19]. The degree of overall peripheral microvascular disease has been shown to correlate with severity of both clinical neuropathy and degree of nerve fiber loss [15]. In summary, in-vivo data highlights both distal vascular and peripheral nerve abnormalities associated with DPN and that these abnormalities are likely to be interrelated. Despite the above findings and possible mechanisms supported by animal model data, the causative pathophysiological changes that give rise to the broad spectrum of clinical neuropathic observations (as well as the occurrence of painful- rather than painless-DPN) remain somewhat elusive.

The CNS in Diabetes

The multi-system, multi-organ consequences relating to changes in glycemic levels that are bought about by diabetes are known to have implications for the status and functioning of the brain. Stroke risk increases by a factor of 2–3 times, the ability to recover function following stroke is known to be impaired, and a general early brain-aging process is thought to be associated with mild cognitive decline [20–22]. In terms of the spinal cord, post-mortem evidence gathered in the 1960s and 1970s showed generalized atrophy, demyelination, and gliosis [22, 23]. All of the aforementioned brain and spinal complications have been reported in studies involving people with diabetes but without definition of the presence or absence of DPN. It is thus apparent that hyperglycemic and/or hypoglycemic events do provide ‘insults’ that directly affect the CNS at multiple levels within the general context of diabetes.

In-vivo evidence of the different aspects of CNS involvement in many diseases that affect the brain or spine, can often now be gleaned by the use of modern imaging modalities, such as x-ray Computerized Tomography (CT), x-ray digital subtraction angiography, Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), non-x-ray ultrasound (albeit difficult within the confines of the cranium), and Magnetic Resonance Imaging (MRI).

Magnetic Resonance Neuroimaging Biomarkers

Since the inception of MRI and the publication of an image of capillary-tubes of water in 1973 [24] a vast number of developments, technique inventions, and clinical implementations have unfolded in the context of imaging in-vivo [25]. Today, MRI is very often the diagnostic modality of choice in the clinical setting when searching for the presence or absence of many different types of pathology, having applications in all organ systems. The fundamental contrast mechanisms in standard clinical imaging are based on relative proton densities, T1- and T2-relaxation time properties, the latter 2 of which are reliant on the parenchymal structure and chemical environment of water and fat protons. Water and, to a lesser extent fat, are the dominant molecules that give rise to the MR signal and thus underlie basic image information content. It is these properties (proton density, T1, and T2) that facilitate the key high detection sensitivity to the presence of different or abnormal tissues that MRI affords. Not only can many pathologies be visualized, giving good anatomical localization, but perhaps the major advance that still continues to develop at a truly amazing rate is the ability of MR to demonstrate and often quantitate many aspects of physiological function. When coupled with the nonionizing nature of MRI that constitutes a low risk to the patient, the abundance of various types of informative data makes the use of MRI an obvious choice for the provision of potential biomarkers in experimental studies as well as yielding high value in routine clinical use. The relative noninvasive nature also points to its suitability for use in follow-up studies and, with scanning resources permitting, studies involving large sample sizes that may be multi-center. In the field of MRI, many new techniques have been initially introduced as applications to imaging of the brain and spine, making MR a potential ideal candidate in the search for CNS abnormalities associated with DPN.

Detailing the vast number of contrast mechanisms that can be harnessed in the context of studying the CNS is beyond this article and can be found elsewhere [25]. However, the types of scan that have hitherto been used to investigate the status of the CNS in DPN are outlined below:

3-Dimensional T1-Weighted Imaging

The T1 of parenchyma is dependent upon tissue structure. It is often termed the spin-lattice relaxation time as, historically, it relates to the time taken for protons to interact and dissipate energy to the overall lattice of a structure. The more fluid the protons are, the longer it takes for them to interact and for their energy to dissipate to the lattice and thus the longer the T1 of that tissue becomes. In the brain, grey matter (containing neuronal cell bodies), white matter (containing myelinated axons), and cerebrospinal fluid

(CSF) have significantly different T1 energy 'relaxation' times. Standard images are often acquired as a set of 2-dimensional slices, where the nominal slice thickness is approximately 5–10 times the in-plane spatial resolution. However, modern clinical neuroimaging technique often encodes the data at high spatial resolution in all 3 dimensions, resulting in a 3-dimensional (3-D) dataset. These 3D, T1-weighted datasets used in conjunction with suitable segmentation algorithms, provide an affective means of separating out and monitoring the absolute volumes of grey and white parenchyma and CSF.

fMRI

fMRI utilizes the Blood Oxygen Level-Dependent (BOLD) effect [26]: as synapses and neurons 'fire', and use energy transferring electrical impulses, oxygenated blood is converted to de-oxygenated blood. In response to the need for a pool of this energy source, localized capillary-bed arterial flow is increased. Although oxygen is extracted, the supply-response results in an overall increase in the local concentration of oxygenated blood. Oxygenated blood is paramagnetic whereas deoxygenated blood is diamagnetic. The change in the resultant magnetic properties alter what is termed the T2*-relaxation time within the vascularized parenchyma. The MR signal detected using imaging sequences such as the gradient echo (and variants thereof) can be weighted by the local $T2^*$-relaxation time. Differences in signal that result from BOLD effect are small (typically 1 %–5 %) and so brain states of neuronal 'activation' caused by the application of a stimulus to promote the desired cerebral response are typically sampled numerous times to improve detectability. Signals following the application of a stimulus are statistically compared with signals resulting from a different brain state, acquired with either no stimulus being present or in conjunction with the application of a stimulus designed to evoke a different function, thereby producing a comparative 'contrast' between brain states [27].

Dynamic Susceptibility Contrast Perfusion

Dynamic susceptibility contrast (DSC) perfusion can assess the passage of blood through the parenchymal bed [28]. With this method, an exogenous bolus of 'blood labelling' contrast is injected intravenously. This consists of a gadolinium-chelate, a rare-earth metal, whose properties perturb local magnetic susceptibility. A series of dynamic images monitor the bolus passage through a slice: the signal drops due to reduction in T2* during the arterial phase then recovers as the bolus washes through. Information regarding bolus transit-time, relative blood volume (rCBV), and flow (rCBF) can be estimated, representing different aspects of cerebral parenchymal perfusion.

Proton MR Spectroscopy

Proton MR spectroscopy (^{1}H-MRS) provides information regarding moieties that contain hydrogen nuclei (protons) in addition to those of water and fat [25]. Due to their different molecular surroundings (subject to differential electron shielding), the hydrogen nuclei resonate at different frequencies resulting in different spectral peaks. Common intracranial resonances can be assigned to: *myo*-Inositol (mI), found in glial cells; Choline (Cho) containing compounds predominantly found in cell walls and often used as a marker of cellular turnover / degeneration; Creatine (Cr+PCr) representing the total energy pool, which exhibits stability except in, for example, necrotic regions; γ-aminobutyric acid (GABA), Glutamate and Glutamine (Glx), representing the MR-visible GABA neurotransmitter / metabolic pathway cycle (inhibitory and excitatory components) and N-Acetyl groups (predominantly N-Acetyl Aspartate or NAA), which have been shown to be largely confined to neuronal cell bodies and axons and can be interpreted as a putative marker of neuronal integrity and function. It should be noted that, as with standard imaging, spectral resonances can represent concentrations (proton density-weighted) or can be weighted by, for example, molecular environment and T2, that can alter differentially for different metabolites, due to the presence of pathology [29]. In terms of NAA, a low density can imply neuronal loss whereas low T2-weighted signal has been found to correlate with clinical neurological function and is capable of recovery [30]. The most common method of spectral spatial localization is the 'single-voxel' technique where the desired signal emanates from the intersection of 3 selective slices, forming the voxel under investigation. Voxel sizes of between 2 and 27 cm^3 are typical and thus have limited spatial specificity. The GABA resonance coincides with that of Cr and technically demanding specific 'spectral editing' techniques have to be invoked to enable its identification [31].

Diffusion Tensor Imaging and Tractography

Diffusion tensor imaging (DTI) and tractography can provide indicative models of the connectivity of axonal tracts within the CNS [28, 32]. Diffusion of water results from slow self-propelled molecular motion (random-walking) associated with the molecules' own energy. If not contained or restricted, diffusion from an initial single source will form a sphere. However, the imposition of a barrier, such as the wall of a myelin tract, will change the sphere into an ellipsoid, the main axis of which (resultant diffusion vector) will point parallel with the wall in the direction of unrestricted diffusion, along the tract. Diffusion can be sensitized by the application of motion-encoding gradients [32]. When applied in multiple directions, information regarding the

diffusion vector can be used to model the overall probabilistic connectivity of the resultant ellipsoids corresponding to bundles of axonal fibers that form tracts. Tract modelling is termed diffusion tractography.

Spinal Imaging: Involvement and Early Marker

As stated previously, although spinal abnormalities had been found at autopsy [22, 23], the reports were nonspecific to the presence or absence of DPN. These documented abnormalities could thus be due to diabetes per say or, alternatively they could have been associated with neuropathy, the latter indicating possible extension of the disease beyond the peripheral nerves. To investigate this, a preliminary MR study obtained axial, T2-weighted 2-D images through the spinal cord (giving good cord / CSF differentiation) in patients with DPN, without DPN and controls and cross-sectional cord areas were calculated at 3 levels: lower cervical, upper, and lower thoracic. Significantly smaller cord areas were found at C4/5 and T3/4 in DPN, the paper concluding that data provided evidence for involvement of the spinal cord on MRI [33]. A larger cohort follow-up study confirmed the findings. In addition, when compared with controls (including a hereditary sensory motor neuropathy disease-control group), subclinical DPN patients that were clinically asymptomatic but had abnormalities on peripheral neurophysiological assessment indicated significantly lower mean cord area compared with those without evidence of DPN. This paper concluded that implied cord atrophy (it was a cross-sectional study) appeared to be an early phenomenon, present even in sub-clinical DPN [34]. Lesions in the spinal cord may result in pain syndromes: in some patients with severe painful-DPN, there may be little in the way of abnormalities on clinical examination or electrophysiological assessment despite evidence of marked abnormalities in somatosensory evoked potentials within the spinal cord [35]. Thus, the caudal aspect of the CNS does appear to demonstrate abnormalities that are concomitant with the presence of both early and established DPN.

Beyond the Cervical Spine: Axonal Pathways to the Thalamus and Cortex

As the spinal cord forms the caudal portion of the CNS, involvement in the neuropathic process raises the question as to whether abnormalities terminate at that level or extend further via the spinothalamic tracts through the brainstem towards the thalamus and then onwards to the sensory cortex and associated intracranial pathways. Very preliminary data from small sample sizes (8 subjects with painless-DPN and 6 volunteers without diabetes) has illustrated the use of MR tractography based on high angular-resolution DTI as a potential method of investigating the integrity and extent of axonal fiber tracts in the context of DPN [36]. Data suggested that the total number of modeled fibers connecting the brainstem with the somatosensory cortex showed a trend towards a decrease in the DPN group. However, larger subject numbers are required to determine whether this technique can provide evidence of involvement of spinothalamic and/or thalamocortical axonal pathways, thereby shedding light on the nature and extent of the neuronal tract degeneration previously observed within the cervical spine [34].

The Sensory Gateway to the Brain

The ascending spinothalamic neurons terminate in the Ventroposterior Lateral (VPL) thalamic sub-nucleus, which then projects input to the cranial aspects of the brain, including the somatosensory cortex. The thalamus is thus often thought of as the sensory gateway to the brain and as such, its function plays a crucial role in sensory processing and signal modulation [37]. Information provided by ^{1}H-MRS regarding the resonance attributed to NAA has been shown to be a useful marker of neuronal integrity and function [25]. Studies have utilized ^{1}H-MRS to interrogate the neurochemistry within the thalamus in the context of DPN [38–40]. In 1 study, spectra were acquired from the thalamus in 18 subjects with type-1 diabetes (8 with no DPN and 10 with DPN) and 6 age and sex-matched healthy controls without diabetes [38]. Two spectra were acquired using different acquisition parameters: (I) at short echo time giving peak areas that reflect metabolite concentrations and (II) at long echo time giving peak areas that are subject to T2-weighting, (which has been shown in other pathologies to be a marker of neuronal function [30]). Significantly lower mean NAA/Cho resonance area ratio was observed at long echo time in the DPN group compared with those from patients without DPN and healthy controls. No significant group differences were present at short echo time, although a significant correlation between NAA level and neuropathy score was identified. In a larger follow-up study comprising 110 patients with type-1 diabetes (20 no DPN, 30 sub-clinical DPN, 30 painful DPN, and 30 painless DPN) and 20 healthy controls without diabetes, spectra were again acquired at both short and long echo time in the thalamus and additionally in the primary somatosensory cortex (S1) [39]. As in the previous study, thalamic long echo time spectra identified abnormalities involving NAA: with a lower NAA/Cr area ratio in the painless DPN group compared with other groups, whereas at short TE, no group differences were identified. Conversely, in the sensory cortex, there were no significant between-group differences in any metabolite ratios at long echo time whereas at short echo time

there was significantly lower mean NAA in the painless DPN group (when compared with both the no-DPN group and group without diabetes). These findings underline that differences can be detected using different spectroscopic acquisition techniques (with long and short TE) and care needs to be taken with interpretation. The findings from this study are consistent with the occurrence of thalamic neuronal dysfunction and cortical loss of neuronal cell bodies (atrophy) in the same groups with painless DPN. In terms of the lack of significant thalamic depletion in NAA density within the thalamus, data from small numbers (7 patients with DPN vs 7 volunteers without diabetes) from a study performed at a different center is in agreement [41]. However, in a further study, short echo-time spectra were acquired from 3 regions including the thalamus from 26 diabetics (12 with and 14 without chronic pain), a lower mean thalamic NAA was found in the diabetic group with pain compared with the diabetic group without pain [40]. These conflicting findings between ^{1}H-MRS studies may reflect sample size considerations or perhaps highlight the need for standardization of spectroscopic data acquisition techniques.

Perfusion can also reflect metabolism as well as baseline vascular supply. Data from a DSC-based perfusion assessment in a cohort of 18 subjects with type-1 diabetes (No DPN=6, painful DPN=5, painless DPN=7) and 5 subjects without diabetes showed that the VPL region of the thalamus was associated with lower rCBV in painless DPN and higher rCBV in painful DPN compared with the no-DPN group and the group without diabetes [42••]. This may imply that hypervascularity is present in patients with painful DPN whilst hypovascularity is a feature of the thalamus in patients with painless DPN. Similar increases in thalamic perfusion have been demonstrated in the streptozotocin-induced rat model of diabetic pain [43]. Of particular note is that animal models of painful-DPN reporting electrophysiological hyperexcitability to various peripheral stimuli (in-keeping with allodynic or hyperalgesic states) *also* show high thalamic VPL electrical impulse activity even when nerve input to the brain has been terminated by transection of the cervical spinal cord [44]. The latter supports the hypothesis that the brain may generate activity in the absence of peripheral input that may lead to the sensation of a pain state. Further *in-vivo* data is required to support this in the clinical context.

Higher Brain Areas: the Pain-Processing Matrix

Studies based on fMRI and PET have led to the characterization of a normative network of brain areas that consistently activate in response to pain, forming a 'pain matrix' [45]. These cortical and sub-cortical brain network nodes include the thalamus as well as the primary and secondary somatosensory cortices (S1 & S2), the insular cortex (IC), the ACC, and the prefrontal cortex (PFC) [46]. These regions are thought to be responsible for discriminating location and intensity of painful stimuli together with affective pain processing [47, 48]. Activation of the lateral thalamus, S1, S2, and IC are thought to be related to sensory-discriminative aspects of pain processing [49]. The basal ganglia, amygdala, cerebellum, hippocampus plus other regions can also be involved and pain perception appears to be associated with a complex connected matrix comprising many functional areas that may interact with each other as well as with the lower levels within the nervous system. Functional MRI may be a useful tool with which to investigate these complex, potentially interactive functional processes in normal subjects. The inclusion of potential neuropathic alterations to the pain matrix adds further to complex investigational demands and these must be realized when inferences are being made.

Using fMRI, a preliminary study [50, 51] which comprised 18 subjects with type-1 diabetes (6 no DPN, 6 painful DPN, and 6 painless DPN) tested the feasibility of monitoring the brain's response to the presentation of an acute thermal stimulus to the foot in the context of DPN. Preliminary analysis showed that subjects with no DPN had greater BOLD response than those with painless DPN. Subjects with painful DPN showed significantly greater response than those with painless DPN. The primary sensory cortex, lateral frontal and cerebellar regions were involved. Negative correlation was also reported between BOLD response in both the thalamus and left parietal lobe and overall neuropathy score. Group differences occurred within the frontal lobe (high/ level perception/cognitive function), the cerebellum (processing speed action), and the thalamus as well as in the sensory cortex. Although similar brain regions were activated in this study with those that comprise the 'pain matrix', there were some clear differences in brain activation patterns. This suggests that the normal network is altered in painful DPN. A similar thermal stimulation fMRI study comprising subjects with type-2 diabetes (11 painful DPN, 11 painless DPN and 11 controls without diabetes) also reported differences between groups: increased BOLD response in the painful DPN group and reduced BOLD response in the painless DPN group compared with controls [52]. In terms of pronounced activation in the painful group, areas identified included the ACC, medial thalamus, anterior-insula, sensory cortices and lentiform nucleus (LN).

Subjectivity associated with pain perception as well as the different forms of clinical symptoms known to be present in DPN may lead to a high degree of between-subject variance, highlighting the need for careful characterization. The individuals' pain matrix, obtained via fMRI itself, may provide unique input to such approaches and the problem of neuropathy stratification.

In the ^{1}H-MRS study by Sorensen et al [40] short echo time spectra acquired from the anterior cingulate cortex (ACC) showed no group differences, suggestive of no apparent neurochemical changes in this constituent of the pain matrix. In the dorsolateral prefrontal cortex (DLPFC) they reported lower NAA and Cr in those with diabetes compared with those without, with no specific differences assigned to the presence or absence of neuropathy.

The status of neurotransmitter balance may be important in DPN. Preliminary data from 7 patients with noninsensate DPN and 7 subjects without diabetes in a study that used spectral editing to investigate GABA-Glx resonances found lower GABA and higher Glx-levels in the posterior insula [41]. No such differences were observed in either the thalamus or the ACC. The authors inferred that the excitatory-inhibition neurotransmitter balance was altered within the posterior aspect of the insula, part of the overall pain-matrix. The potential importance of this finding warrants further investigation.

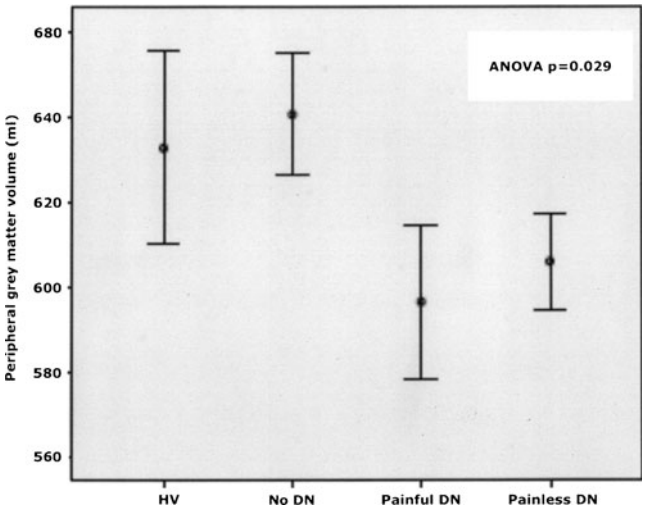

Fig. 1 Statistically significant lower group mean cortical grey matter volumes have recently been reported from 3D volumetric MR studies in patients with DPN when compared with groups without DPN [54]

Intracranial Atrophy?

Changes in parenchymal volume within the CNS are important as neuronal regeneration is not likely once atrophy has occurred. Strong relationships have been reported between brain volumes and walking outcomes in elderly patients with and without DPN [53•]. Within the last year, detailed assessments of intracranial component volumes have been presented from a cohort of 54 subjects with type-1 diabetes (23 with no-DPN, 16 with painful, and 15 with painless DPN)) and 18 subjects without diabetes [54••]. Grey matter changes suggestive of atrophy were found in DPN compared with non-DPN groups. Cortical grey matter differences were found despite correcting for age, sex, and the degree of diabetic retinopathy, suggesting the DPN was the main factor (Fig. 1). Significant localized cortical grey matter differences were apparent in areas associated with somatosensory perception (precentral, postcentral, and supramarginal gyri). The inference of a sensory-cortical atrophy in DPN supports the previous observation of a lower NAA level (at short echo time) that was taken to imply an atrophic process observed in the sensory cortex, in patients with DPN [39].

Summary and Conclusions

From numerous reports it is becoming apparent that there are indeed changes within the CNS that, on a cross-sectional study basis, appear to be concomitant with the evolution of painful and painless DPN. Magnetic Resonance imaging and spectroscopic studies have documented:

(I) spinal cord cross-sectional area differences, notably in subclinical DPN;
(II) changes suggestive of atrophy in the sensory cortices;
(III) hyper-perfusion in painful DPN and hypo-perfusion in painless DPN within the thalamus;
(IV) neurochemical changes that suggest abnormal neuronal thalamic function;
(V) neurochemical changes that suggest and neuronal atrophy in the primary sensory cortex;
(VI) alterations to GABA-Glx spectral resonances and the excitatory-inhibition neurotransmitter balance and
(VII) complex variance in the BOLD response to an external painful stimulus in DPN.

MR imaging and spectroscopy techniques have the potential to further elucidate the nature of CNS involvement in DPN. Imaging may help us to unravel one of the fundamental unanswered questions - where can the primary pathophysiology of the painful symptomatology of DPN be found? Magnetic Resonance may also address the question of whether involvement at different CNS levels is due to ‘die-back’ phenomena following the development of peripheral pathology or is due to direct insults at the various levels, or a combination of both. Perhaps the key to unlocking this lies in the acquisition of prospective, longitudinal, multi-level, and multi-functional imaging data. It is hoped that in-vivo MR imaging may lead to development of more rational therapies to help reduce the burden of DPN.

Compliance with Ethics Guidelines

Conflict of Interest Iain D. Wilkinson declares that he has no conflict of interest.

Dinesh Selvarajah declares that he has no conflict of interest.
Marni Greig declares that he has no conflict of interest.
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Elaine Boland declares that she has no conflict of interest.
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Solomon Tesfaye declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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